

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-567

ADMINISTRATIVE DOCUMENTS

Time Sensitive Patent Information Pursuant to 21 C.F.R. 314.53
for NDA #21-567

A. PATENTS

- (1) U.S. Patent No.: 5,849,911
Expiration Date: April 9, 2017
Type of Patent: Drug Substance
Patent Owner: Novartis Finance Corporation
- (2) U.S. Patent No.: 6,087,383
Expiration Date: December 21, 2018
Type of Patent: Drug Substance
Patent Owner: Bristol-Myers Squibb Co.

Bristol-Myers Squibb Co. is the exclusive licensee of U.S. Patent No. 5,849,91

B. DECLARATION

The undersigned declares that the above stated United States Patent Nos. 5,849,911 and 6,087,383 cover the drug substance which is the subject of the present New Drug Application.

David M. Morse
Signature of Authorized Person

DAVID M. MORSE
Name of Authorized Person

PATENT COUNSEL
Title of Authorized Person

October 4, 2002
Date

EXCLUSIVITY SUMMARY for NDA # NDA 21-567 SUPPL # N/A
Trade Name: REYATAZ™
Generic Name: atazanavir
Applicant Name: Bristol-Myers Squibb
HFD- 530
Approval Date: June 20, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED? Yes

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

- a) Is it an original NDA? YES / X / NO / /
b) Is it an effectiveness supplement? YES / / NO / X /

If yes, what type(SE1, SE2, etc.)?

- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

- d) Did the applicant request exclusivity?

YES / X / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / X /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES / / NO / X /

If yes, NDA # Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____
NDA # _____
NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- (a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # _____ YES /___/
NO /___/ Explain: _____ !
!
!
!
!
Investigation #2 !
!
IND # _____ YES /___/
NO /___/ Explain: _____ !
!
!
!
!
!

- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____ !
!
!
!
!
Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____ !
!
!
!
!
!

- !
- (c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/

NO /_X_/

If yes, explain: _____

/S/

Signature of Preparer

Title: Regulatory Management Officer

June 20, 2003

Date

/S/

Signature of Office or Division Director

6/20/03

Date

cc:

Archival NDA

HFD-530 /Division File

HFD-Vasavi Reddy /RPM

HFD-093/Mary Ann Holovac

HFD-104/PEDS/T.Crescenzi

Form OGD-011347

Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

NDA #21-567: Atazanavir Sulfate Capsules

Request for Exclusivity

Upon approval of these New Drug Applications ("NDAs"), Bristol-Myers Squibb Company (the "Applicant") hereby claims five (5) years of market exclusivity for atazanavir sulfate capsules _____ pursuant to 21 USC §355 (j)(5)(D)(iii) and 21 CFR §314.108 (b)(4).

In support of this request for exclusivity and in accordance with 21 CFR. §314.50(j):

The Applicant certifies to the best of its knowledge that each of the clinical investigations submitted with this NDA meets the definition of "new clinical investigation" set forth in 21 CFR. §314.108 (a).

2. The Applicant certifies that it has thoroughly searched the scientific literature and, to the best of its knowledge, the information publicly available does not provide a sufficient basis for the approval of these NDAs without reference to the new clinical investigations contained in the NDAs. The public information is insufficient because it does not include any clinical studies to date which demonstrate the endpoints of the registrational studies, AI424-034 and AI424-043, that are included in these NDAs. Therefore, in the Applicant's opinion, the clinical investigations contained in this NDA are essential for the approval of this NDA.
3. The Applicant certifies that the studies were conducted and sponsored by BMS, under IND No. _____ for atazanavir sulfate (ATV, BMS-232632).

Cynthia F. Piccirillo

Cynthia F. Piccirillo
Director, Regulatory Science
Bristol-Myers Squibb Company

12/13/02

Date

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA #NDA: 21-567 Supplement # N/A Circle one:

HFD-530 Trade and generic names/dosage form: REYATAZ™ (atazanavir capsules) 100mg, 150mg, & 200mg

Action:

Applicant : Bristol-Myers Squibb Therapeutic Class: Protease Inhibitor

Indication(s) previously approved: N/A

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Proposed indication in this application: REYATAZ™ indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION. IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___ Yes (Continue with questions) ___ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___ Neonates (Birth-1month) ___ Infants (1month-2yrs) Children (2-12yrs) ___ Adolescents (12-16yrs)

- ___ 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- ___ 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- X 3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
- ___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- ___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- X c. The applicant has committed to doing such studies as will be required.
- ___ X (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
- ___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- ___ 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- ___ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ☐ Yes ☒ No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from: Kendall Marcus, M.D., Medical Reviewer
(e.g., medical review, medical officer, team leader)

Vasavi Reddy, RPh, Regulatory Project Manager

June 20, 2003

Signature of Preparer and Title

Date

cc: Orig NDA/BLA # 21-567
HFD- 530/Div File
NDA/BLA Action Package
HFD-960/ Peds Team
(revised 1-14-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 4-7337

APPEARS THIS WAY
ON ORIGINAL

NDA #21-567 Atazanavir Capsules
Atazanavir Powder for Oral Use

§21 CFR 314.55 Certification for Deferral/Partial Waiver of Pediatric Use

Under the provisions of 21 CFR 314.55, Bristol-Myers Squibb Company (BMS) is requesting deferral of the requirement for inclusion of complete data in these NDAs to assess the use of atazanavir in combination with other antiretroviral agents for the treatment of pediatric HIV-infected patients and provide appropriate dosing recommendations in this population. Furthermore, BMS requests a waiver of the requirement for pediatric HIV-infected patients <3 months of age (discussed below). BMS acknowledges that, per the requirements, atazanavir is a drug product which is likely to provide a meaningful therapeutic benefit over existing treatment for HIV-infected pediatric patients, may be used for the proposed indication in the pediatric population, and complete evaluation is necessary to adequately identify the appropriate dosing recommendations for this population.

BMS has developed a suitable dosage form for younger pediatric patients, i.e. atazanavir Powder for Oral Use. Data to support registration of this dosage form is provided in . In addition, NDA #21-567 includes data to support registration of lower strengths of the atazanavir capsule dosage form, suitable for dosing lower weight pediatric patients who are able to swallow capsules.

This submission includes an interim report for data available at the time of the NDA datalock from ongoing study AI424-020 (PACTG 1020 A), "A Phase I/II Open Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS-232632) in Combination Regimens in Antiretroviral Therapy (ART) – Naïve and Experienced HIV-Infected Infants, Children and Adolescents". These data evaluate the safety, pharmacokinetics and antiviral efficacy in 44 patients treated under this protocol. Study AI424-020 is being conducted under IND No. sponsored by the Pediatric AIDS Clinical Trial Group, with support from BMS. This study is evaluating the use of atazanavir as part of a combination antiretroviral regimen in four cohorts:

Group 1 - minimum of 18 subjects, 3 months and 1 day to 2 years of age (less than or exactly 730 days), receiving the powder formulation of atazanavir, in combination with two nucleoside analogue reverse transcriptase inhibitors (NRTIs*);

Group 2 - minimum of 18 subjects, 2 years and 1 day (731 days or more) to 13 years of age, receiving the powder formulation of atazanavir, in combination with two NRTIs*;

Group 3 - minimum of 18 subjects, 2 years and 1 day (731 days or more) to 13 years of age, receiving the capsule formulation of atazanavir, in combination with two NRTIs*;

Group 4 - minimum of 18 subjects, 13 years and 1 day to 21 (not including the 22nd birthday) years of age, receiving the capsule formulation of atazanavir, in combination with two NRTIs*.

{*Abacavir (ABC, abacavir sulfate, Ziagen) has been excluded as one of the NRTIs options for the subject's regimen under PACTG 1020 A.}

(See protocol for complete study details, found in Appendix 1 of the interim study report, Document Control Number 930002965, included in Item 8 of NDA #21-567.)

At the time of this submission, dosing recommendations have not been identified for any of the cohorts. However, as previously agreed with the Agency at the Pre-NDA meeting on September 4, 2002, BMS will provide any additional data which become available at the time of the Safety Update submission (projected in February 2003).

Since the predominant laboratory abnormality prevalent in atazanavir-treated patients is hyperbilirubinemia, and neonates sometimes have elevated bilirubin, BMS recommends that atazanavir is not used in the age cohort of pediatric patients <3 months of age to avoid increased risk of this event. **Therefore, we request a *partial waiver* of the requirement to study atazanavir in HIV-infected patients < 3 months of age under 314.55 (c)(3)(iii) as use of atazanavir may be unsafe in this specific age group.** The proposed package insert, reflects this recommendation (see DOSAGE AND ADMINISTRATION, Pediatric Patients).

BMS has diligently pursued the identification of a suitable dosage form and provided support for the initiation of the pediatric study at the same time as the adult Phase III trials were initiated. Therefore, the deferral request is made on the basis that it is not appropriate to delay registration for use of atazanavir in adult HIV-infected patients until complete data are available for the pediatric HIV-infected population. The partial waiver request is made on the basis that use of atazanavir in the age group <3 months of age may be unsafe in this specific age group.

BMS certifies that the atazanavir development program has diligently pursued the evaluation of atazanavir in the pediatric HIV-infected population and data will be submitted to these NDAs at the earliest possible time.

Cynthia F. Piccirillo

Cynthia F. Piccirillo
Director, Regulatory Science
Bristol-Myers Squibb Company

CERTIFICATION: DEBARRED PERSONS

Bristol-Myers Squibb Company certifies that it has not used and will not use the services of any person listed as debarred as of the most recent FDA Debarment List (May 9, 2003) under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 355 (a) or (b)] in any capacity in connection with this Application for Atazanavir Capsules.

Cynthia F. Piccirillo

Cynthia F. Piccirillo
Director, Regulatory Science
Bristol-Myers Squibb Company
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-1996
(203)677-7625

June 16, 2003
Date

Bristol-Myers Squibb Company

Atazanavir
BMS-232632

Financial Disclosure

Financial Disclosure

Atazanavir
BMS-232632

190 page(s) excluding cover page

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).


Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	AI424007 Table A	
	AI424007 Table B	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Steven Schnittman, MD	TITLE Vice President, Global Development Champion
FIRM / ORGANIZATION Bristol-Myers Squibb Company	
SIGNATURE 	DATE 11/18/02

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH**

DATE: 6-19-03

FROM: Debra Birnkrant, M.D.
Director, Division of Antiviral Drug Products, HFD-530

TO: Division File for NDA 21-567

SUBJECT: Division Director's Memorandum for NDA 21-567
for ReyatazTM (atazanavir) for the Treatment of HIV infection

This memorandum is written in support of the approval of ReyatazTM (atazanavir), a once-daily protease inhibitor for the treatment of HIV-1 infection in naïve and limited treatment-experienced subjects. This regulatory action is based on the favorable risk/benefit profile of the drug as determined by a multidisciplinary review of the totality of the data contained in NDA 21-567. This memorandum will focus on the two pivotal clinical trials containing up to 48 weeks of clinical data and an overall risk/benefit assessment addressing issues related to indirect hyperbilirubinemia, PR prolongation and lipid effects.

BACKGROUND:

A NDA for atazanavir was submitted in December, 2002. It received a 6-month priority review because it was the first once-a-day protease inhibitor that allowed for a lower pill burden and it had favorable effects on lipid parameters compared to other drugs in the protease inhibitor class. An Antiviral Drugs Advisory Committee was held on May 13, 2003, to discuss BMS' application for atazanavir; the advisory committee voted unanimously to approve atazanavir for treatment of HIV infection following extensive discussion.

As further background, NDA 21-567 contained a multitude of clinical biopharmaceutic and pharmacokinetic studies, and many clinical studies of which there were two principal studies, 034 and 043 which examined the use of atazanavir in combination with nucleoside backbones in comparison to control arms containing widely used and potent antiretrovirals, efavirenz and lopinavir/ritonavir, respectively. Efficacy data from a third phase 3 trial, study 045, examined atazanavir in highly treatment-experienced patients. This data will not be used to support the approval of atazanavir because only limited data were submitted in the original NDA submission and a different regimen of

atazanavir was studied, namely a ritonavir-boosted regimen. Adequate phase 2 evaluation was also conducted in order to determine dose selection for the phase 3 trials. See review by Dr. Jenny Zheng, Clinical Biopharmaceutics reviewer.

TRIAL RESULTS: EFFICACY

Study 034(n= 810), was an international, multicenter, randomized, double-blind, double-dummy 48-week trial where subjects were randomized to receive either atazanavir 400 mg q d or efavirenz with fixed dose zidovudine/lamivudine. Subjects were treatment naïve and other pertinent entry criteria included HIV RNA \geq 2000 copies per ml and CD4 counts > 100 cell/mm³ or > 75 cells/mm³ if no prior AIDS events. Virologic response through week 48 revealed the following results: subjects randomized to atazanavir had a response rate of 67 % compared to 62% on the efavirenz arm for the endpoint proportion below LOQ=400 copies/ml. Examining the results of an analysis of proportion below 50 copies/ml, both treatment arms had lower than expected results: atazanavir had a response rate of 32% compared to a rate of 37% on the efavirenz containing arm. A lower than expected rate below 50 copies/ml for both treatment arms may be due to the use of the more sensitive Roche Amplicor HIV-1 Monitor Assay, version 1.5 used in the clinical trial. Please see microbiology review by Dr. Lisa Naeger. Regarding mean CD4 cell count increase from baseline in treated subjects, there was an increase of 176 cells on the atazanavir arm compared to 160 cell increase on the control arm.

Study 043(n=300) was the second principal trial contained in NDA 21-567. It was also an international, multicenter, randomized study that was open-label and examined atazanavir compared to lopinavir/ritonavir, each in combination with two nucleoside reverse transcriptase inhibitors, in limited treatment-experienced subjects who had failed a prior protease-containing regimen. The trial was designed as a 48-week study, but only 24-week data were submitted for review in the original NDA submission. The prior duration of antiretroviral drugs by class was PIs, 140 weeks, NRTIs, 180 weeks and NNRTI, 85 weeks. Results of the trial revealed that although atazanavir was active in suppressing virus, it was less so compared to lopinavir/ritonavir. Specifically, the proportion of subjects with HIV RNA < 400 copies per ml at week 24 was 57% in the atazanavir arm compared to 76% in the control arm. Immunologically, mean CD4 cell count increase from baseline in atazanavir treated subjects was 101cells/mm³ compared to a 121 cell increase on the control arm.

The question arose as to why the treatment outcomes on atazanavir were less than that of the control arm in treatment-experienced subjects. Potential answers include pk and resistance issues. From a pk perspective, C_{min} values for atazanavir, which are thought to play a role in the activity of protease inhibitors in general, may not be high enough in treatment experienced subjects. If the C_{min} could be increased, as with ritonavir boosting of lopinavir in the control arm, then it is possible that more mutations may be required to develop resistance resulting

in treatment-experienced subjects having better outcomes. This approach is being evaluated in study 045.

The issue of treatment outcome deserves further comment. When study 043 was being designed, the review division recommended that boosted lopinivir be used as the control because we wanted to see how well atazanavir performed against the most potent marketed protease inhibitor. After reviewing the data from 043, it appears that atazanavir performed similarly to an unboosted protease inhibitor, as would be expected. Although atazanavir has a unique resistance mutation, I50L, that may develop in naïve subjects, and confers enhanced susceptibility to other drugs in the class, it develops mutations along a more classic pathway in treatment experienced subjects that is similar to other drugs in the class, except for boosted lopinivir. Whereas atazanavir is unique in naïve subjects, lopinivir/ritonavir has a genetic threshold for development of resistance that is higher than other PIs. Also, see Drs. Marcus, Hammerstrom, Zheng and Naeger's review for a complete analysis of the efficacy, clinical pharmacokinetics and microbiology data.

TRIAL RESULTS: SAFETY

The safety database contains a total of 2229 subjects who received at least one dose of atazanavir. Of the 2229 subjects exposed to atazanavir, more than 1500 HIV infected subjects received at least one dose of atazanavir. The proposed dose of 400 mg per day was received by 683 treatment naïve subjects and 363 treatment experienced subjects. Safety issues identified in the principal studies are related to the following four key areas: hyperbilirubinemia, effects on ECG, lipid effects and drug interactions. Comments related to resistance will also be briefly discussed.

Hyperbilirubinemia

All grades of hyperbilirubinemia were observed in the majority of patients receiving atazanavir; indirect hyperbilirubinemia comprised the majority of hyperbilirubinemia. Grades 3-4 hyperbilirubinemia were observed in about one-third of subjects, however treatment discontinuation was rare for this common, yet reversible adverse event. This adverse event was extensively evaluated by the applicant and it was determined that it was due to inhibition of UGT 1A1, which is similar to indinavir-associated hyperbilirubinemia and that seen in Gilbert's syndrome. Hepatotoxicity, manifested by elevations of ALT/AST were uncommon and comparable to control arms in clinical trials. Patients co-infected with hepatitis B/C were more likely to develop elevated liver associated enzymes. Thus, labeling for atazanavir advises that caution should be exercised when administering atazanavir to patients with hepatic impairment. It should also not be unexpected to see additional cases of hepatotoxicity once more patients receive atazanavir after it is marketed, given that only a few thousand subjects received it in clinical trials.

Cardiac Effects

In vitro studies showed that atazanavir had effects on rabbit Purkinje action potentials, weak inhibition of sodium currents and moderate inhibition of calcium currents. It also produces weak inhibition of IKr current (HERG) and IKs potassium current in in vitro assays. Toxicology studies in dogs did not reveal any direct drug-related effects on cardiac function. The potential for cardiac effects was further studied in human subjects because of concerns about QT prolongation, based on in vitro findings. BMS conducted a placebo-controlled study, 076, to examine effects of atazanavir on ECG parameters. When Fridericia's correction formula was utilized because of an increase in heart rate seen with atazanavir, clinically significant changes in QTc were not observed. Further, subjects receiving atazanavir in phase 2/3 trials did not appear to have an excess of cardiac adverse events related to QT prolongation as compared to subjects in control arms. With regard to PR prolongation, dose dependent prolongation was observed in subjects receiving atazanavir, however, findings were comparable to control arms containing other PIs. There is a section in the labeling addressing the effects of atazanavir on the ECG and wording in the warnings section advising that co-administration with drugs primarily metabolized by CYP3A4 may result in increased plasma concentrations of the co-administered drug, such as calcium channel blockers that could lead to increased therapeutic and adverse effects. In labeling, it states that the dose of diltiazem should be reduced by half because of the pharmacokinetic interaction leading to additive toxicity.

Lipid effects

Unlike other drugs in the PI class, atazanavir had a positive effect on certain lipid parameters. Whereas increases in LDL cholesterol were seen in comparator arms in 034 and 043, LDL cholesterol did not increase in subjects receiving atazanavir. Triglycerides followed the same pattern, that is no increase in the atazanavir arms and increases in the control arms. Unfortunately, lipodystrophy was still seen in clinical trials as were the class effects of hyperglycemia and diabetes. It is also unknown whether improvement in lipid parameters will translate into lack of cardiovascular effects with chronic use.

Drug Interactions

Atazanavir is a competitive inhibitor of CYP3A4. As such, drug-drug interactions between atazanavir and other CYP3A4 substrates or drugs that inhibit CYP3A4 are potentially clinically significant. The labeling for atazanavir contains wording to address this important issue. See review by Dr. Jenny Zheng.

Resistance

Almost 80% of atazanavir-resistant clinical isolates from trials of treatment naïve subjects who were virologic failures developed the I50L mutation, a unique atazanavir mutation; development of this mutation ranged from 12-80 weeks. Examination of the atazanavir-resistant isolates containing this mutation showed an average 10.9 fold change from baseline for atazanavir, but an increased

susceptibility to approved protease inhibitors (PIs). Mutations developing in treatment-experienced subjects proceeded along a common PI resistance pathway and included I84V, G48V, A71V, L90M, V82A/T/F, N88S/D, and M46I; these were highly cross resistant to other PIs. If PI mutations are present at baseline, then the treatment effect of atazanavir is likely to be diminished. Consequently, phenotypic and genotypic testing may be indicated in treatment experienced patients.

RISK/BENEFIT ASSESMENT:

To date, there are six approved protease inhibitors on the market. What sets atazanavir apart from them is once daily dosing and positive effects on lipid parameters. These characteristics are extremely important to patient adherence and ultimately, treatment effect. Although a number of adverse events were identified in the atazanavir database, both hyperbilirubinemia and PR prolongation are reversible and can be easily monitored. The risk/benefit profile of atazanavir is favorable with antiviral activity comparable to efavirenz and nelfinavir in treatment naïve subjects. Regarding activity in treatment experienced subjects, atazanavir performed as well as could be expected compared to other unboosted PIs in the class with a similar safety profile as naïve subjects. As is recommended in public health treatment guidelines, the use of phenotypic and genotypic testing in treatment-experienced subjects may be useful; this is especially true when considering the use of atazanavir in an HIV cocktail. There are clearly experienced subjects who would benefit from a once daily protease inhibitor with positive effects on lipid parameters. Consideration should be given to the need to boost pharmacokinetic parameters in treatment-experienced subjects and this question will be answered in Study 045.

In sum, I am in full support of the approval of atazanavir for use in combination with other antiretroviral agents for the treatment adults with HIV-1 infection.

PROPOSED PHASE 4 COMMITMENTS:

Post-marketing commitments will be requested in the following areas: chemistry, microbiology, biopharmaceutics, pharmacology/toxicology and clinical. The will be finalized prior to approval. See below.

Post-approval Commitments

Microbiology:

1. Submit analysis of protease cleavage sites in ATV- resistant patients from ongoing studies 034, 043 and 045.

Protocol submission - Not Applicable

Study start - Ongoing

Final report submission within 12 months of the date of this letter.

2. Test the activity *in vitro* of atazanavir against multiple clinical isolates of non-clade B subtypes of HIV-1 and HIV-2.

Protocol submission - Not Applicable

Study start - Ongoing

Final report submission within 12 months of the date of this letter.

Pharmacology/Toxicology:

3. Complete ongoing carcinogenicity studies in mice and rats and submit final reports.

Protocol submission - Completed

Study start - Ongoing

Final reports submission within 9 months of the date of this letter.

Clinical Pharmacology:

4. Conduct drug-drug interaction study to explore dosing recommendations for the coadministration of atazanavir and nevirapine and of atazanavir/ritonavir and nevirapine.

Protocol submission within 6 months of the date of this letter.

Study start within 10 months of the date of this letter.

Final report submission within 30 months of the date of this letter.

5. Evaluate the pharmacokinetics of atazanavir when co-administered with histamine H2 receptor antagonist.

Protocol submission within 3 months of the date of this letter.

Study start within 7 months of the date of this letter.

Final report submission within 24 months of the date of this letter.

6. Evaluate the pharmacokinetics and safety of atazanavir when coadministered with interferon and ribavirin in patients infected with hepatitis C virus.

Protocol submission within 13 months of the date of this letter.
Study start within 18 months of the date of this letter.
Final report submission within 36 months of the date of this letter.

7. Determine, *in vivo*, the extent to which atazanavir inhibits CYP1A2 or CYP2C9, preferably with warfarin, or with theophylline.

Protocol submission within 9 months of the date of this letter.
Study start within 12 months of the date of this letter.
Final report submission within 27 months of the date of this letter.

8. Conduct a pharmacokinetic study of atazanavir in subjects with renal impairment to allow the determination of dosing for this population..

Protocol submission within 4 months of the date of this letter.
Study start within 8 months of the date of this letter.
Final report submission within 39 months of the date of this letter.

Clinical

9. Assess the long term antiviral efficacy and safety of atazanavir in ARV treatment naive and stable switch patients through the conduct of studies -034, -044, -041 and -067.

Protocol submission - Completed
Study start - Ongoing
Final reports submission within: 12 months of the date of this letter for study -034;
24 months for studies -044, -041; 27 months for study -067.

10. Assess the efficacy and safety of atazanavir when pharmacokinetically boosted with low dose ritonavir in protease inhibitor treatment naive patients.

Protocol submission within 3 months of the date of this letter.
Study start within 6 months of the date of this letter.
Interim 24 week report submission within 24 months of the date of this letter.

11. Using objective measurements (e.g., DEXA and CT scanning, etc.) evaluate the role of atazanavir in fat redistribution through 96 weeks of therapy through the conduct of studies -034/-077 (DEXA and CT scan) and -043 (CT scan).

Protocol submission - Completed
Study start - Ongoing
Final report submission within 39 months of the date of this letter.

12. Evaluate the suspected protease inhibitor class-associated effects of fat redistribution and metabolic abnormalities through the conduct of studies -034/-077 and -043.

Protocol submission - Completed

Study start - Ongoing

Final report submission within 12 months of the date of this letter.

13. Follow a cohort of patients who failed on ATV treatment and developed the I50L mutation on new physician-selected PI regimens for 48 weeks compared to an NNRTI-failure/PI-naïve patient cohort and determine treatment response, baseline genotypes and phenotypes, and genotypes and phenotypes of virologic failures.

Protocol submission within 9 months of the date of this letter.

Study start within 12 months of the date of this letter.

Final report submission within 36 months of the date of this letter.

Chemistry:

14. A test (USP<781>) for optical rotation will be developed by fourth quarter 2003. Data will begin to be collected for all commercial batches. Once sufficient data are generated, the data will be reviewed to determine a numerical acceptance criterion and drug substance specification will be updated accordingly.

Final submission: Within 12 months of the date of this letter (with the annual report)

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/s/

• Debra Birnkrant
6/20/03 12:10:40 PM
MEDICAL OFFICER

Mark Goldberger
6/20/03 01:55:08 PM
MEDICAL OFFICER

Team Leader's Memorandum

NDA: 21-567

Drug and Indication: ReyatazTM (atazanavir) capsules for the treatment of HIV-1 infection in combination with other antiretroviral agents

Dose: 400 mg once daily with meals

Submission received: December 20, 2002

Date of MO review: June 5, 2003

Date of Memorandum: June 5, 2003

This New Drug Application for atazanavir, a new azapeptide protease inhibitor for the treatment of HIV-1 infection, was submitted by Bristol Myers Squibb Company on December 20, 2002 and was assigned a 6-month priority review. The proposed indication is based on the surrogate endpoint analyses of plasma HIV RNA and CD4 cell counts in antiretroviral treatment naïve and antiretroviral treatment experienced HIV-infected subjects enrolled in controlled studies of 48 and 24 weeks, respectively.

In support of this indication, the applicant submitted the results of two principal trials (AI424034 and AI424043), two phase 2 trials (AI424007/041 and AI424008/044), and over 40 clinical pharmacology/pharmacokinetics/drug interaction studies. In addition, the applicant has submitted 16 weeks preliminary efficacy and 24 weeks safety results of a ritonavir-boosted atazanavir regimen for a small number of patients enrolled in the ongoing study AI424-045 in highly treatment experienced patients who have failed at least two regimens containing drugs from all three classes. The primary efficacy measure in study 034 was the proportion of patients who achieved and maintained HIV RNA <400 copies/mL through 48 weeks using Roche Amplicor® HIV-1 MonitorTM Assay, 1.0 and 1.5 versions. In study 043, the primary efficacy endpoint was time averaged change from baseline in log₁₀ HIV RNA level through 24 weeks.

The two principal studies in this NDA, AI424034 and AI424043, one conducted in treatment naïve and another in treatment experienced patients, compared antiretroviral activity of atazanavir in combination with background therapy to efavirenz or lopinavir/ritonavir, respectively.

Study AI424-034 was a double-blind, multi-center, 48-week trial enrolled 810 patients (antiretroviral treatment naïve) who were randomized to atazanavir 400 mg daily or efavirenz 600 mg daily. Patients also received a fixed dose combination of lamivudine 150 mg and zidovudine 300 mg twice daily. Included centers were in North and South

America, Europe, Asia, and Africa. Randomization was stratified by baseline HIV viral load of $<30,000$ or $\geq 30,000$ copies/mL.

A second trial AI424-043 was an open-label, multi-center trial that enrolled 300 HIV-infected patients who had failed a prior protease-inhibitor-containing regimen. Patients were randomized to atazanavir 400 mg daily or lopinavir/ritonavir 400/100 mg twice daily. Patients also received optimized NRTI background therapy. Sixty-eight study centers were located in North and South America, Europe, and Australia.

In study 034 at week 48, 67% of patients in the atazanavir treatment arm achieved and maintained HIV RNA <400 copies/mL compared to 62% patients in the efavirenz treatment arm. Estimated difference between the treatment arms was 5.0% and the 95% confidence interval for the difference was (-1.5, 11.6). In study 043, based on the analysis of mean change from baseline in HIV RNA at week 24, there was a possibility that atazanavir could be 0.43 log copies/mL inferior to lopinavir/ritonavir. Based on the analysis of HIV RNA percent below LOQ of 400 at week 24, 47% (70/150) of patients in the atazanavir treatment arm achieved and maintained HIV RNA <400 copies/mL compared to 65% (98/150) patients in the lopinavir/ritonavir treatment arm. Estimated difference between the treatment arms was -19.0% and the 95% confidence interval for the difference was (-29.7, -7.9). Based on the submitted data, the antiviral efficacy of atazanavir in combination with 2 NRTIs in treatment naïve patients was demonstrated in study 034 and was supported by two smaller phase 2 trials. In treatment experienced patients, the results of study 043 did not support a conclusion that antiviral effect of atazanavir was similar to lopinavir/ritonavir but it was concluded that atazanavir-containing regimen did appear to have a treatment effect (see discussion of historical comparisons below).

The mean increase in CD4 cell counts from baseline was similar across all treatment regimens and was comparable between atazanavir and efavirenz, nelfinavir, or lopinavir/ritonavir in treatment naïve and experienced patients.

A total of 737 healthy subjects were enrolled in the clinical pharmacology studies. Of 2425 HIV-infected subjects who were treated in the clinical trials, 1596 received at least one dose of atazanavir in combination with other antiretroviral therapies. Six hundred eighty-three treatment naïve patients received atazanavir in phase 2 and phase 3 trials and 373 treatment-experienced patients received atazanavir 400 mg or ritonavir boosted atazanavir for at least 24 weeks.

The majority of adverse events were Grade 1-2 in both treatment naïve and experienced patients. The most commonly reported adverse events were infection, nausea, headache, vomiting, diarrhea, abdominal pain, rash, and fever. A greater incidence of nausea, lipodystrophy, jaundice, scleral icterus, rash, and pain in extremity was reported in treatment naïve and treatment experienced patients who received atazanavir than comparator treatment. The primary safety concerns are related to the effect of atazanavir on ECGs, hyperbilirubinemia, and drug interactions.

The number of CDC Class C events was small. Three treatment-experienced patients in the atazanavir treatment group developed CDC Class C events (two developed candida infection and one *Mycobacterium tuberculosis*) and three patients in the lopinavir/ritonavir treatment group developed candida infection, HIV wasting, or *pneumocystis carinii* infection.

Detailed discussion of atazanavir safety and efficacy is provided in the medical and statistical review of this new drug application. I am in agreement with the conclusions of the primary reviewers that this application should be approved and that atazanavir efficacy was demonstrated in the treatment naïve and treatment experienced HIV-infected patients when atazanavir was given as a part of antiretroviral regimen. This application was presented at the Antiviral Drugs Advisory Committee meeting on May 13, 2003. Based on the presented information, the Committee unanimously recommended approval of atazanavir for the treatment of HIV-1 infection, when used in combination with other antiretroviral agents.

The once daily atazanavir treatment may provide the advantage of a lower pill burden and convenience of once daily dosing, and therefore, may improve compliance with antiretroviral therapy. However, it should be emphasized that strict compliance with the once daily regimen is important because if daily doses are missed it may lead to prolonged periods of lower atazanavir plasma levels and possibly promote the emergence of resistance.

The following issues warrant comment at the time of the regulatory action:

Safety

Drug Interactions

Atazanavir is metabolized in the liver by CYP3A and is a competitive inhibitor of CYP3A at clinically relevant concentrations. In addition, it is also an inhibitor of UGT1A1. Drugs that induce CYP3A4 activity such as rifampin may be expected to lower atazanavir plasma concentration and an opposite effect on atazanavir plasma concentration may be expected if atazanavir is coadministered with drug that inhibit CYP3A4 such as ritonavir. In addition, coadministration of atazanavir and drugs metabolized by CYP3A4 (e.g. calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, and sildenafil) could result in increased plasma concentration of other drugs and therefore, induce serious adverse effects. Atazanavir may also be a substrate and a weak inhibitor of P-glycoprotein and appears to inhibit CYP1A2 and CYP2C9.

Hyperbilirubinemia

The most frequently observed laboratory adverse event with an overall incidence rate of approximately 90% was hyperbilirubinemia, which was primarily due to increases in unconjugated bilirubin. Grade 3-4 elevations were observed in approximately 40% of patients. The data from phase 2 studies suggest that this toxicity is dose related. The incidence was higher in the group of patients receiving atazanavir at a dose greater than 400mg/day compared to patients receiving atazanavir at a dose <400 mg/day. Only a

small number of patients (3% to 7%) who received the 400 mg dose had elevations of total serum bilirubin > 5x ULN. Approximately 2% of patients discontinued treatment because of hyperbilirubinemia or jaundice. Grade 3-4 elevations of bilirubin were rarely associated with grade 3-4 elevations in hepatic transaminases. Jaundice and/or scleral icterus was reported in approximately 15% of atazanavir treated patients. Based on the submitted safety information, the hyperbilirubinemia associated with atazanavir treatment did not appear to be associated with an increased incidence of hepatocellular toxicity relative to efavirenz or PIs used in clinical trials.

It is important that patients be monitored during treatment to be able to detect any hepatotoxicity, especially patients co-infected with hepatitis B and C.

Effect on electrocardiogram

The effects of atazanavir on cardiac action potential and ion currents were evaluated in *in vitro* assays and in clinical studies that included HIV-infected patients and healthy volunteers. *In vitro* studies demonstrated that atazanavir weakly inhibits sodium and potassium (HERG) currents and moderately inhibits calcium currents. Atazanavir was also found to cause a modest prolongation of the action potential in rabbit Purkinje fiber assays. QTc prolongation may lead to increased risk for potentially fatal ventricular arrhythmia (torsade de pointes). The relationship between prolongation of the PR interval and the risk for development of serious and life-threatening cardiovascular events is less clear.

In order to further evaluate the effects of atazanavir 400 mg and 800 mg on the QTc and PR interval, the applicant conducted a placebo-controlled pharmacokinetic study in 72 healthy subjects. However, the study did not include a positive control nor included atazanavir doses higher than 800 mg. When the QTc interval was corrected for the heart rate using an appropriate formula it appeared that atazanavir did not cause QTc prolongation in this study (in which subjects were not taking other potentially interacting drugs). First degree AV block (PR>200 msec) was reported in 14% of patients who received atazanavir 400 mg and 59% of patients who received atazanavir 800 mg in this trial. The changes in the PR interval were not associated with clinical events.

In HIV infected patients, ECGs were evaluated in five clinical trials. The incidence of QTc prolongation during treatment was low. However, PR prolongation >200 msec was seen in 54 of 920 (5.9%) who received atazanavir 400 mg daily. Second- or third-degree AV block was not reported in these trials.

It appears that there is a low risk for potential serious arrhythmia or high degree AV block associated with atazanavir 400 mg. There is limited information available on the potential interaction between atazanavir and other drugs that prolong the QTc and PR interval. These effects should be clearly described in the labeling for atazanavir and should require further monitoring in the postmarketing phase, as they could alter the risk-benefit relationship once the drug is used in various settings outside clinical trials.

Study results in treatment experienced patients

The virologic effects of atazanavir in combination therapy were less than those of lopinavir/ritonavir in treatment experienced patients. The contribution of atazanavir to the treatment regimen was evaluated by retrospective comparison to results from studies assessing the efficacy of dual nucleoside regimens. It was suggested that the difference observed between regimens that contained atazanavir in combination with two nucleosides and two nucleosides alone was large enough to support the conclusion that atazanavir has some antiviral effect in treatment experienced patients.

Resistance

Based on genotypic analyses of atazanavir-resistant isolates selected *in vitro*, it appears that I50L, N88S/D, A71V, I84V and M46I substitutions play a role in atazanavir resistance. In addition to *in vitro* resistance studies, resistance to atazanavir was evaluated in clinical isolates from patients in clinical trials. The clinical isolates were obtained from patients who had virologic failure on atazanavir containing regimens and had decreased susceptibility to atazanavir of ≥ 2.5 fold. Most of PI treatment naïve patients who developed resistance to atazanavir during treatment had isolates containing an I50L substitution alone or in combination with A71V. Phenotypic analysis of the clinical isolates containing the I50L mutation showed atazanavir-specific resistance, which coincided with increased susceptibility to the six-marketed protease inhibitors. This may preserve future treatment options regarding treatment with other protease inhibitors. In treatment-experienced patients, the I50L substitution was much less likely to occur and atazanavir resistance resulted from other mutational pathways with decrease susceptibility to multiple PIs. Isolates from treatment-experienced patients treated with atazanavir or atazanavir/saquinavir acquired mutations, such as I84V, L90M, A71V, N88S/D or M46I. These mutations were associated not only with atazanavir resistance but also with decreased susceptibility to all other approved protease inhibitors.

Pediatric study

Forty-four pediatric patients with median 9 years of age (range 7 months to 20 years) were enrolled into a PACTG open-label, pharmacokinetic and safety study. Seventeen patients had discontinued study treatment as of July 17, 2002. Eight discontinuations were due to adverse events: two due to hyperbilirubinemia, two due to vomiting, two due first degree heart block, one due to pancreatitis, and one due to non-treatment related cardiomyopathy. The most frequently reported laboratory abnormality was hyperbilirubinemia reported in 14 patients (32%). At present, the available data are not sufficient to support dosing recommendations for atazanavir to be used in children.

Effect on lipid parameters

The results of phase 3 trials confirmed previous findings that atazanavir had a lesser effect on total cholesterol, LDL, and triglycerides than efavirenz, nelfinavir or lopinavir/ritonavir in both treatment naïve and treatment-experienced patients. However, it appears that atazanavir had no effect on development of lipodystrophy, generalized weight gain or weight loss; these events were reported with similar frequency in the atazanavir and comparator groups.

Risk/benefit assessment

Risk/benefit assessment for atazanavir included demonstrated efficacy of atazanavir based on the suppression of viral load and increases in CD4 cell counts in treatment naïve patients when atazanavir in combination with background therapy was compared to efavirenz and nelfinavir. It was also determined that in treatment experienced patients atazanavir may provide a treatment benefit. With regard to safety, adverse events related to treatment with atazanavir are well described and documented in the clinical trials. In addition to once daily dosing, atazanavir has a lesser effect on lipid parameters than comparator PIs or efavirenz. In treatment naïve patients, because of the unique resistance profile it appears that susceptibility to other PIs will be preserved if resistance to atazanavir develops; in addition, susceptibility to atazanavir is generally maintained in the presence of resistance to up to two PIs. The overall assessment of benefits and risks associated with atazanavir supports the use of atazanavir as a component of antiretroviral regimens in the treatment of HIV-1 infection.

Labeling discussions were focused on Microbiology, Clinical Pharmacology, Indication and Usage, Warning, and Adverse Reactions Sections of the Package Insert for atazanavir to include balanced presentation of resistance, safety and efficacy data in treatment naïve and treatment experienced patients.

The following are postmarketing commitments for the atazanavir:

1. Submit analysis of protease cleavage sites in ATV- resistant patients from ongoing studies 034, 043 and 045.
 - Protocol submission - Not Applicable
 - Study start - Ongoing
 - Final report submission within 12 months of the date of this letter.
2. Test the activity in vitro of atazanavir against multiple clinical isolates of non-clade B subtypes of HIV-1 and HIV-2.
 - Protocol submission - Not Applicable
 - Study start - Ongoing
 - Final report submission within 12 months of the date of this letter.
3. Complete ongoing carcinogenicity studies in mice and rats and submit final reports.
 - Protocol submission - Completed
 - Study start - Ongoing
 - Final reports submission within 9 months of the date of this letter.
4. Conduct drug-drug interaction study to explore dosing recommendations for the coadministration of atazanavir and nevirapine and of atazanavir/ritonavir and nevirapine.
 - Protocol submission within 6 months of the date of this letter.
 - Study start within 10 months of the date of this letter.
 - Final report submission within 30 months of the date of this letter.

5. Evaluate the pharmacokinetics of atazanavir when co-administered with histamine H2 receptor antagonist.
 - Protocol submission within 3 months of the date of this letter.
 - Study start within 7 months of the date of this letter.
 - Final report submission within 24 months of the date of this letter.
6. Evaluate the pharmacokinetics and safety of atazanavir when coadministered with interferon and ribavirin in patients infected with hepatitis C virus.
 - Protocol submission within 13 months of the date of this letter.
 - Study start within 18 months of the date of this letter.
 - Final report submission within 36 months of the date of this letter.
7. Determine, in vivo, the extent to which atazanavir inhibits CYP1A2 or CYP2C9, preferably with warfarin, or with theophylline.
 - Protocol submission within 9 months of the date of this letter.
 - Study start within 12 months of the date of this letter.
 - Final report submission within 27 months of the date of this letter.
8. Conduct a pharmacokinetic study of atazanavir in subjects with renal impairment to allow the determination of dosing for this population.
 - Protocol submission within 4 months of the date of this letter.
 - Study start within 8 months of the date of this letter.
 - Final report submission within 39 months of the date of this letter.
9. Assess the long term antiviral efficacy and safety of atazanavir in ARV treatment naive and stable switch patients through the conduct of studies -034, -044, -041 and -067.
 - Protocol submission - Completed
 - Study start - Ongoing
 - Final reports submission within: 12 months of the date of this letter for study - 034; 24 months for studies -044, -041; 27 months for study -067.
10. Assess the efficacy and safety of atazanavir when pharmacokinetically boosted with low dose ritonavir in protease inhibitor treatment naive patients.
 - Protocol submission within 3 months of the date of this letter.
 - Study start within 6 months of the date of this letter.
 - Interim 24 week report submission within 24 months of the date of this letter.
11. Using objective measurements (e.g., DEXA and CT scanning, etc.) evaluate the role of atazanavir in fat redistribution through 96 weeks of therapy through the conduct of studies -034/-077 (DEXA and CT scan) and -043 (CT scan).
 - Protocol submission - Completed
 - Study start - Ongoing
 - Final report submission within 39 months of the date of this letter.
12. Evaluate the suspected protease inhibitor class-associated effects of fat redistribution and metabolic abnormalities through the conduct of studies -034/-077 and -043.

Protocol submission - Completed

Study start - Ongoing

Final report submission within 12 months of the date of this letter.

13. Follow a cohort of patients who failed on ATV treatment and developed the I50L mutation on new physician-selected PI regimens for 48 weeks compared to an NNRTI-failure/PI-naïve patient cohort and determine treatment response, baseline genotypes and phenotypes, and genotypes and phenotypes of virologic failures.

Protocol submission within 9 months of the date of this letter.

Study start within 12 months of the date of this letter.

Final report submission within 36 months of the date of this letter.

14. A test (USP<781>) for optical rotation will be developed by fourth quarter 2003. Data will begin to be collected for all commercial batches. Once sufficient data are generated, the data will be reviewed to determine a numerical acceptance criterion and drug substance specification will be updated accordingly.

Final submission: Within 12 months of the date of this letter (with the annual report)

Stanka Kukich, M.D.
Medical Team Leader, DAVDP

Concurrence:
HFD-530/divDirector/Dbirnkrant

cc:NDA 21-567
HFD-530/MO/KMarcus

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Stanka Kukich
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Debra Birnkrant
6/20/03 03:28:24 PM
MEDICAL OFFICER

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 2, 2003

TO: Debra Birnkrant, M.D., Director
Division of Antiviral Drug Products
HFD-530

VIA: Vasavi Reddy, Regulatory Health Project Manager
Division of Antiviral Drug Products
HFD-530

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
(DSRCS), HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication
Support (DSRCS), HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for atazanavir, NDA
21-567

The attached patient labeling (clean copy) represents part of the revised risk communication materials for atazanavir, NDA 21-567. We have simplified the wording, made it consistent with the PI, and removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Please call us if you have any questions. Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

9 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

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this page is the manifestation of the electronic signature.

/s/

Jeanine Best
6/9/03 03:22:34 PM
CSO

Toni Piazza Hepp
6/10/03 08:31:45 AM
DRUG SAFETY OFFICE REVIEWER

Office of Drug Safety

Memo

To: Janice Soreth
Director, Division of Anti-Infective Drug Products
HFD-520

From: Denise Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

CC: Vasavi Reddy, R.Ph.
Project Manager, Division of Anti-Infective Drug Products
HFD-520

Date: April 29, 2003

Re: ODS Consult 01-0193-4; Reyataz [Atazanavir Capsules and Oral Powder]
100 mg, 150 mg, 200 mg, _____; NDA#s: 21-567 _____

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

This memorandum is in response to the March 10, 2003 request from your Division for a re-review of the proprietary name, Reyataz. In our consult, dated November 1, 2002 (ODS consult # 01-0193-2), DMETS did not have any objections to the use of the proprietary name Reyataz. DMETS also reviewed the container labels, carton and package insert labeling in our review dated March 10, 2003 (ODS consult # 01-0193-3). Revised labels and labeling were not submitted with this consult, therefore DMETS refers to the DMETS recommendations listed in the aforementioned labeling review.

Since the initial Reyataz proprietary review, the DMETS Expert Panel identified five additional proprietary names, not previously reviewed as having the potential to cause name confusion with Reyataz. The Panel identified Ceptaz as a potential look-alike to Reyataz. _____, and the modifier _____

were also identified as having potential sound-alike similarities to Reyataz. The new drug applications (NDAs) for _____ and the abbreviated new drug application (ANDA) for _____ were withdrawn in 1971, 1980, and 1994 respectively. Therefore, these products will not be addressed in this review.

- Ceptaz and Reyataz may look-alike depending upon how they are scripted. Ceptaz is a third-generation cephalosporin antibiotic indicated for the treatment of infections caused by susceptible organisms. The products share the same last three letters (taz) which increases the look-alike potential. However, they have different dosing intervals (every 8 or every 12 hours vs. daily) and routes of administration (intravenous or intramuscular vs. oral). Additionally, they do not share overlapping strengths (1 gram or 2 grams vs. 100 mg, 150 mg, 200 mg, _____). The potential for name confusion between Ceptaz and Reyataz is minimal based on the different product characteristics.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

The panel also noted that the modifier _____, *** sounded similar to Reyataz. This is a modifier used for the proposed name _____. DMETS reviewed the proposed proprietary names _____ and did not recommend use of the proprietary names. However, DMETS must consider the potential for name confusion between Reyataz and these names, specifically the modifier _____ because the final disposition of _____ is still pending and final action has not been taken on the NDA. The beginning letters (_____ vs. Re) and the ending letters (_____ vs. taz) of _____ and Reyataz may sound similar depending upon how they are pronounced. The second syllable of each name is phonetically different and helps to distinguish the two names. The modifier _____ represents an orally disintegrating tablet formulation which, disintegrates within seconds after placement on the tongue, allowing it to be swallowed with or without water. It is unlikely that prescribers will prescribe _____ the modifier, without the proprietary name- _____. However, _____ prescription was misinterpreted as Reyataz, the different dosing interval (three times a day vs. daily) and recommended dose of each product (10-20 mg TID vs. 400 mg daily) would help to differentiate the products. The differences in the dosing interval, recommended dose, and the improbability that the modifier will be ordered without the proprietary name would decrease the potential risk of medication errors between Reyataz and _____.

Based on the differences between Reyataz and Ceptaz or the modifier _____ the potential for name confusion is minimal. Therefore, we have no objections to the use of the proprietary name, _____ Reyataz.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

Denise Toyer
5/1/03 02:42:27 PM
PHARMACIST

Carol Holquist
5/1/03 02:47:44 PM
PHARMACIST



Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20816
Tel (301) 594-5384, FAX (301) 594-5494

Memorandum

DATE: March 5, 2003

FROM: Shari L. Targum, M.D., Medical Officer
Division of Cardio-Renal Drug Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Deputy Director
Division of Cardio-Renal Drug Products, HFD-110
Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products, HFD-110

TO: Vasavi Reddy, Regulatory Project Manager, Division of Antiviral Drug Products, HFD-530
Kendall Marcus, M.D., Medical Officer, Division of Antiviral Drug Products, HFD-530

SUBJECT: Drug effect on PR and QT intervals with risk assessment

NAME OF DRUG: Atazanavir (BMS-232632)

TRADE NAME: N/A

FORMULATION: ORAL (capsules)

RELATED APPLICATIONS: IND # _____

APPROVED INDICATIONS: N/A

SPONSOR: Bristol Myers Squibb

DOCUMENTS AVAILABLE FOR REVIEW: 1. Draft Medical Officer Cardiac Safety Review (received 2/24/03); 2. Sections 5.8.7 and 5.9 (p.319-350) from Section 5: Summary of Safety Results (sponsor).

DATE CONSULT RECEIVED: January 27, 2003

DATE CONSULT COMPLETED: March 5, 2003

BACKGROUND:

Atazanavir (BMS-232632) is a protease inhibitor developed for the treatment of HIV. I am familiar with atazanavir (ATV) from previous consultations. At the present time, the NDA is under priority review by the Division of Antiviral Drug Products with a planned Advisory Committee discussion on May 13, 2003 and PDUFA goal date of June 20, 2003. HFD-110 has been asked to review the provided data and give a general assessment of: the magnitude of effect of atazanavir on the PR and QT intervals, clinical relevance, and general risk assessment of expected adverse events associated with use of this drug.

There are currently several approved protease inhibitors, including nelfinavir, ritonavir, saquinavir, indinavir, and amprenavir¹, for the treatment of HIV. Atazanavir is a substrate, as well as inhibitor, of cytochrome P450 3A4. This drug is about 79% eliminated via feces (either incomplete absorption or biliary excretion) and about 13% eliminated via the kidneys.

Preclinical Data: Atazanavir was tested *in vitro* at concentrations of 0 (DMSO vehicle), 3, 10, and 30 μ M for effects on rabbit Purkinje fiber action potentials (N=5). There was a dose-dependent increase in mean APD₅₀ (action potential duration at 50% repolarization) and APD₉₀. The maximum % Δ , in the 30 μ M arm, was 24 and 13 for APD₅₀ and APD₉₀, respectively. According to the sponsor, these results translate to four times the C_{max} and 17 times the C_{ss} in man given ATV at 400 mg/day. Other testing revealed: weak inhibition of sodium currents (IC₅₀ > 30 μ M), moderate inhibition of calcium currents (IC₅₀ of 10.4 μ M), weak inhibition of IKr (HERG) (15% at 30

¹ Source: 2002 Physicians' Desk Reference.

μM ; IC50 not established because higher concentrations not tested). The sponsor notes that nelfinavir, saquinavir and lopinavir inhibit IKr with IC50 of 7.9, 17.6, and 22.0 μM , respectively. Neither ATV nor the other protease inhibitors evaluated² inhibited IKs (IC50 > 30 μM).

The Sponsor also notes that no atazanavir-related ECG changes were observed in a 9 month study of dogs given up to 180 mg/kg/day (three times the Cmax and seven times the AUC in man given ATV at 400 mg/day).

Clinical Data:

1. Phase I studies:

Results and analysis from seven studies of ATV effects on ECG parameters are summarized in the draft Medical Officer review.

Two females experienced a delta QTc > 60 msec on ATV 400 mg PO QD. However, no subjects were reported as having a post-dose prolonged QTc (> 450 msec for males, > 470 msec for females).

In Study 040, a 24-subject three-period crossover study of ATV 200, 400 and 800 mg daily, linear regression analysis (Cavg (0-12h) vs. delta PR Max) showed a positive slope (0.0096) and significant 95% confidence interval (0.0060, 0.0133); a linear regression analysis of delta QTc Max vs. Cavg (0-12h) showed a positive slope of 0.0019 and 95% confidence interval of (-0.0001, 0.0039).

2. Phase II/III Studies:

Cardiovascular Clinical Adverse Events: In the draft Medical Officer review, cardiovascular events of all grades were reported with roughly equal frequency among ATV and comparators.

Fifteen cases of syncope are noted; in addition, cases of dizziness are noted. It is recommended that your Division explore these cases in order to ensure that they are unrelated to QTc prolongation/high-grade AV block/underlying arrhythmia.

QTc analyses:

An increase from baseline QTc (30-60 msec) was seen in up to 26% of males given ATV400 in Study A1424043 (compared to 27% of males given the comparator). Depending on the treatment group, zero to 8% of ATV treatment groups (either alone or in combination) experienced on-study > 60 msec increase in QTc from baseline. As noted, the exposure (and N) in males appears to be at least double that seen in females.

Per the draft Medical Officer review, the number and percentage of patients experiencing QTc prolongation were similar among treatment groups, and not increased in ATV compared to other treatment regimens. As expected, the Phase II/III studies involve active controls without a concurrent placebo arm

ISSUES & COMMENTS:

1. ECG findings:

a) PR interval prolongation:

- The definition of "borderline prolonged PR interval" of 201-250 msec is generated by the sponsor and is not a standard definition. The standard definition of first degree AV block is a PR interval > 0.20 seconds (or > 200 msec).³
- The available data suggest a dose-related PR interval prolongation (see Figure 1, as well as draft Medical Officer Review, On-study PR prolongation-All Phase 2/3 Studies). A likely mechanism, given pre-clinical findings, is calcium channel blockade.
- According to the sponsor, the clinical relevance of PR interval >250 msec is unknown. This reviewer agrees. First degree AV block in asymptomatic individuals with appropriate heart rates does not, by itself, require intervention or pose a safety concern⁴.
- Although no cases of other types (2nd or 3rd degree) AV block were reported, its occurrence cannot be excluded based on the available information. The risk of 2nd or 3rd degree AV block is not clear.

² These included: nelfinavir, saquinavir, lopinavir, ritonavir, and indinavir.

³ Many classic textbooks of cardiology can be cited. The reader is referred to Chapter 19: AV block (p.311), from Marriott HJL et al. Advanced Concepts in Arrhythmias, Third Edition. c. 1998, Mosby, Inc.

⁴ It is worth noting that digitalis and verapamil are examples of currently marketed drugs that affect AV node conduction.

- This reviewer might be concerned about higher grades of AV block, particularly in patients with underlying conduction system disease (who are unable to mount a junctional escape rhythm). This reviewer anticipates that such cases will be rare in the pivotal trials (as you currently have a database of about 1000 patients); typically these patients are elderly or have underlying heart disease. Another concern relates to patients on concomitant medication affecting AV node conduction; additive or synergistic effects leading to high-grade AV block cannot be excluded.
- This reviewer would recommend appropriate cautionary language in product labeling.

b) QT prolongation:

- The available data show "signals" based on preclinical studies (APD prolongation, IKr inhibition). Regression analysis from a Phase I study showed a slightly positive slope, with 95% CI that crossed zero.
- The sponsor makes an argument that ATV is less potent than several other protease inhibitors with regard to IKr inhibition. Your Division should review the assay method in order to ascertain whether the IKr assay was performed under identical conditions and using the same cell line. As this reviewer discussed with Dr. John Koerner (pharmacologist, HFD-110), given the assay variability, it is unclear whether the differences in IKr inhibition between nelfinavir, saquinavir and lopinavir (IC50 of 7.9, 17.6 and 22 μ M) are meaningful ones.
- Based on preclinical and clinical signals, this reviewer concludes that a safety risk exists; however, the extent of this risk is difficult to quantify. This reviewer is particularly concerned about individuals with increased susceptibility (due to genetic predisposition, electrolyte imbalances, underlying heart disease, concomitant medication, or conditions where drug metabolism is impaired). If there is a food effect, this will, in addition, increase variability of serum concentrations.
- If other protease inhibitors are also IKr blockers (unclear where APD is prolonged with the other protease inhibitors), this may present a possible explanation for QTc prolongation on ATV being comparable to the other treatment groups. However, this raises the safety question for other protease inhibitors as well.
- It is noted that the QTc findings "remain to be clarified by an ongoing placebo-controlled trial." It is not clear what role this trial will play in the approval or labeling of ATV (given that the drug is currently under priority review).
- Cases of dizziness and syncope should be evaluated for potential relationships to cardiac rhythm disturbances.
- The safety issue of QTc effects would need to be balanced against benefits in the HIV population.
- Effects (serum concentrations) on QTc in renal/hepatic impairment should be evaluated, as well as conditions that will increase serum concentrations of ATV.
- As a cautionary note, Bazett's correction, while widely used, has the limitations of overcorrecting at elevated heart rates and undercorrecting at slow heart rates.

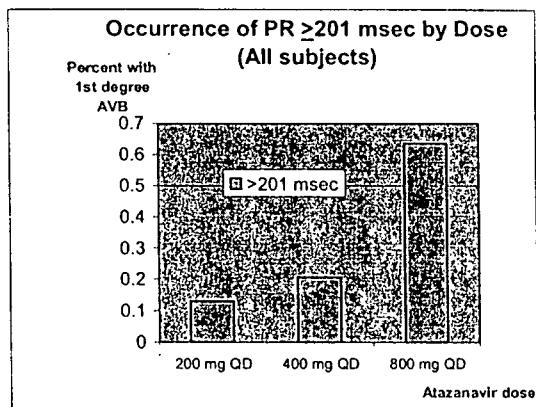
RECOMMENDATIONS:

- Your Division should evaluate this drug, with potentially important benefits in this patient population against safety risks; this reviewer would suggest a trial with morbid-mortal outcomes in order to facilitate this decision.
- The pharmacologic profile of this drug, including metabolism, should be well-understood, as well as scenarios where ATV concentrations rise.
- If ATV is approved, then this reviewer would suggest appropriate cautionary labeling with a recommendations for ECG monitoring.
- Your Division might consider reviewing the other protease inhibitors (thought to be IKr inhibitors) for effects on repolarization as well as cardiac safety.

If you have any further questions please feel free to contact us.

Figures:

Figure 1. First degree AV block by ATV Dose



Source: Section 5: Summary of Safety Results page 323, Table 5.8.7.1A (from Study reports for AI424021, AI424039, AI424040, AI424056, AI424057, AI424058). Results for ATV 300 mg were omitted because no PR prolongation was reported. (N for ATV 200 mg QD=23; N for ATV 400 mg QD = 150; N for ATV 800 mg QD = 22). PR 201-250 and > 250 msec were combined into one category.

Figure 2. Percent of Subjects with Prolonged PR interval for All subjects enrolled in Clinical Pharmacology Studies

Source: Summary of Safety Results, Appendix 5.8.7C. Total number of subjects (not subdivided by gender) is displayed. N Prestudy =705; ATV only =463; ATV Plus = 358; ATV Any = 662; Placebo/other = 116. N is the number of subjects with ECG measurements.

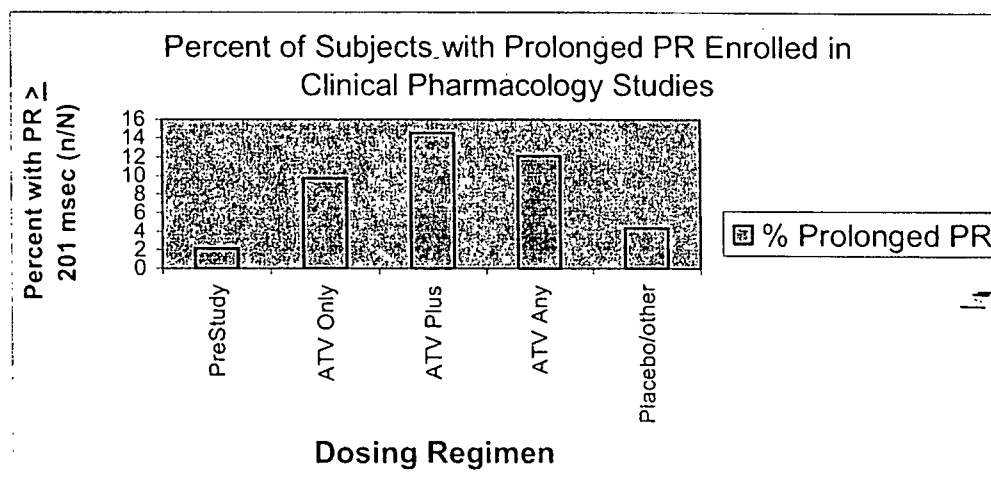
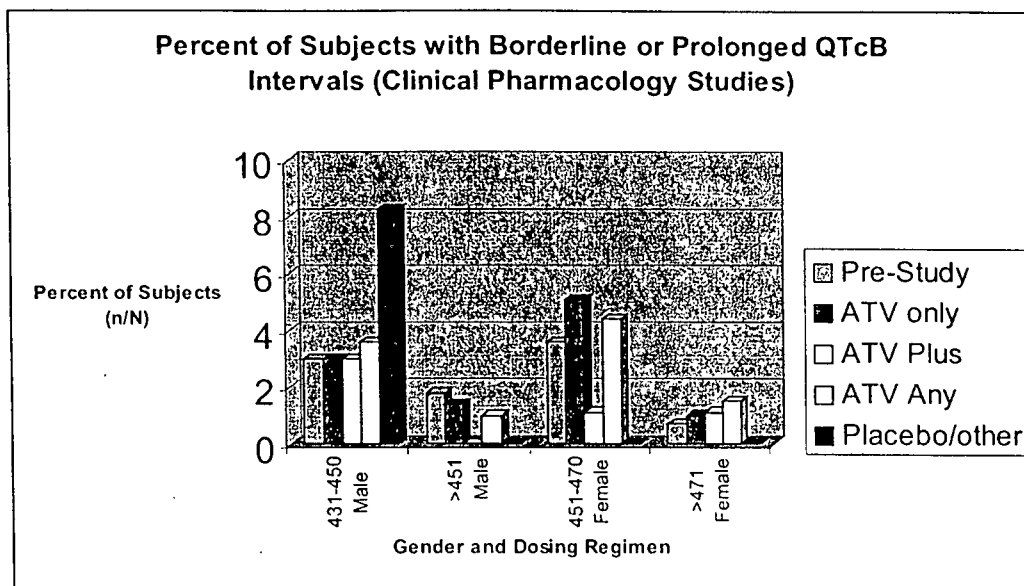
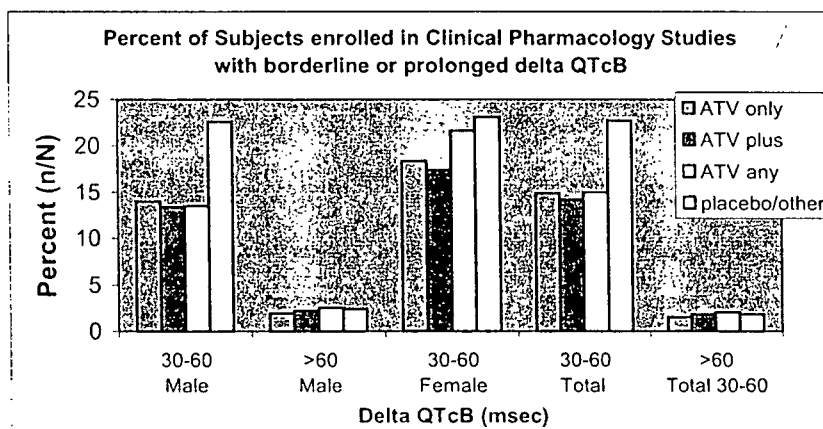


Figure 3. Percent with Borderline or Prolonged QTcB Intervals in Clinical Pharmacology Studies (All Subjects Enrolled)



Source: Summary of Safety Results, Section 5: Appendix 5.8.7A. (N Female Pre-Study =140, ATV only =98, ATV Plus =90, ATV any = 137, placebo/other =32; Male Prestudy N =565, ATV only = 365, ATV Plus = 358, ATV Any = 662, Placebo/other = 116). N = number of subjects with ECG measurements. QTcB=corrected QT via Bazett's formula.

Figure 4. Percent of Subjects with Borderline or Prolonged Delta QtcB for All Subjects Enrolled in Clinical Pharmacology Studies



Source: Summary of Safety Results, Section 5, Appendix 5.8.7B. Total N on ATV only = 463, ATV plus =337, ATV Any =641, Placebo/other = 110. N is the number of subjects with ECG measurements.

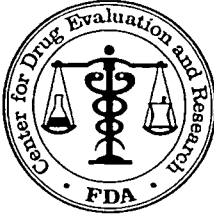
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/s/

Shari Targum
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MEDICAL OFFICER

Norman Stockbridge
3/7/03 12:52:21 PM
MEDICAL OFFICER

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3/7/03 03:09:42 PM
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Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
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Tel (301) 594-5384, FAX (301) 594-5494

Memorandum

DATE: September 13, 2002

FROM: Shari L. Targum, M.D., Medical Officer
Division of Cardio-Renal Drug Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Team Leader
Division of Cardio-Renal Drug Products, HFD-110
Douglas Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products, HFD-110

*Strongly spec = need
for introduction in future
S/L*

TO: Vasavi Reddy, RPh, Regulatory Project Manager, Division of Antiviral Drug Products, HFD-530
Kendall Marcus, M.D., Medical Officer, Division of Antiviral Drug Products, HFD-530

SUBJECT: IND #

NAME OF DRUG: Atazanavir (BMS-232632)

TRADE NAME: N/A

FORMULATION: ORAL (capsules)

RELATED APPLICATIONS: N/A

APPROVED INDICATIONS: N/A

SPONSOR: Bristol Myers Squibb

DOCUMENTS AVAILABLE FOR REVIEW: 1. Submission No. 302-Pre-NDA Background Document, Volume 3, Appendix 5: Electrophysiologic Summary Document (pages 385-571); 2. Protocol A1424-034:A Phase III Study Comparing the Antiviral Efficacy and Safety of BMS-232632 with EFA Virenz; Each in Combination with Fixed Dose Zidovudine-Lamivudine (pages 1-101); 3. Response to FDA Facsimile Dated January 29, 2002 (pages 1-381); 4. Previous HFD-110 consultation (S. Targum).

DATE CONSULT RECEIVED: July 12, 2002

DATE CONSULT COMPLETED: September 12, 2002

BACKGROUND:

Atazanavir (BMS-232632) is a protease inhibitor under development for the treatment of HIV. This Division (HFD-110) has previously been consulted regarding risk and evaluation of PR and QT interval prolongation. In the prior consultation from the Division of Antiviral Drug Products (HFD-530), it was noted "there is a clear dose-related prolongation of PR interval, and less clear prolongation of the QT interval. Over 1000 patients have been dosed with no obvious cardiac events." In this follow-up consultation, this Division is asked to review materials submitted by the sponsor summarizing effect of atazanavir on QT and PR intervals. This Division is specifically asked to address: 1. risk of torsade de pointes with the proposed dosing regimens; and 2. risk of significant cardiovascular events due to PR prolongation; and provide, if needed, any further suggestions.

There are currently several approved protease inhibitors, including nelfinavir, ritonavir, saquinavir, indinavir, and amprenavir¹, for the treatment of HIV. This drug is currently in Phase III of drug development. The proposed dosing regimens are: 400 mg once daily, and in a "ritonavir enhanced" regimen as atazanavir 300 mg and ritonavir 100 mg.

¹ Source: 2001 Physicians' Desk Reference.

The sponsor notes (Protocol amendment 2, Study AI424-034) "BMS-232632 appears to be associated with a dose-related asymptomatic prolongation of PR-interval. These increases were most apparent at the 800 mg dose. BMS-232632 also appears to be associated with dose dependent and concentration dependent increase in the QTc interval. The maximum changes in the PR-interval ranged from 19 to 66 msec and primarily occurred at 2 hours post dose; and the maximum changes in the QTc interval primarily occurred at 6 hours post dose. No subject had a QTc > 500 msec and no subject had an increase in QTc > 60 msec at any dose level. A review of cardiovascular events from Phase II/III studies did not identify any apparent drug-related cardiotoxicity in > 1,000 subjects on clinical studies of BMS-232632."

Preclinical Data: According to the Sponsor; atazanavir was tested *in vitro* at concentrations of 0 (DMSO vehicle), 3, 10, and 30 μ M for effects on rabbit Purkinje fiber action potentials (N=5). There was a dose-dependent increase in mean APD₅₀ (action potential duration at 50% repolarization) and APD₉₀. The maximum % Δ , in the 30 μ M arm, was 24 and 13 for APD₅₀ and APD₉₀, respectively.

Pharmacokinetic Data:

In the prior consultation, a pharmacokinetic study synopsis (Study AI424040) was submitted to this Division (please see prior consultation).

To summarize, this was an open-label, randomized, three-period crossover study where 24 healthy subjects received 200 to 800 mg daily of atazanavir for 5 days with no placebo arm and no washout period.

ECG results from that trial as as follows:

QTc Interval: As seen in Appendix 4E, the mean QTc interval for all groups was < 400 msec; a peak mean QTc was seen 6 hours post-dosing.

A QTc > 430 msec was noted for one male in the 200 mg group (Study Day 15, 6 hours post dose, QTc=441 msec) and one male in the 800 mg group (Study Day 5, 6 hours post dose, QTc=442 msec and 8 hours post dose, QTc=432 msec). No abnormal QTc was noted for the female subjects.

Ten subjects, 9 males and 1 female, were noted to have a change from baseline QTc Max to QTc Max > 30 msec (Table 4C); of these subjects, 5 were in the 800 mg group. The Δ QTc Max in these subjects ranged from 33.5 to 52 msec. The mean change from baseline QTc Max to QTc Max was 12 msec in the 200 mg group, 9 msec in the 400 mg group, and 19 msec in the 800 mg group.

The sponsor performed a linear regression of QTc changes from baseline on measures of drug exposure. All point estimates for the slopes were positive, with an estimated increase in QTc changes from baseline for each additional 1000 ng/mL Cmax ranging between 0.5 and 1.1 msec.

PR Interval: Figure 4D (page 26), mean PR interval vs. Time since dosing, appears to show a dose-related increase in PR interval, with maximum effects in the 800 mg group and at 2-3 hours post-dose. Fifty-eight percent of subjects had 1st-degree AV block on at least one ECG at one or more dose levels; marked PR prolongation (>400 msec) was seen in one female subject in the 800 mg group.

Current Submission:

1. Electrophysiologic Summary Document:

A. Preclinical:

The reviewer discussed results of preclinical testing with Dr. John Koerner (Pharmacologist, HFD-110). The findings were overall positive for nonclinical data based on *in vitro* rabbit Purkinje fiber and *in vivo* dog toxicology study (preliminary conclusion).

In the 2 week dog study, a QT increase was noted at mid and top doses; PR and QRS increases were noted at top dose. At all doses there was weight loss, emesis, plasma electrolyte changes. Animals were sacrificed at top dose due to adverse clinical findings. In the 9 month dog study, there were no EKG effects and no adverse clinical effects; however, the top dose in the 9 month study was lower than in the 2 week study (2 fold).

A concentration-related lengthening in APD90 was noted in rabbit Purkinje fiber testing.

Ion channels: The reviewer did not see a concentration-response curve for effect on HERG or sodium channels to verify effect (see below: the sponsor notes modest activity at high doses). Atazanavir appears to block calcium current; this would not prolong QT.

B. Clinical (summarized):

Results for seven studies (AI424021, AI424039, AI424040, AI424055, AI424056, AI424057, AI424058) were summarized; the first 3 studies evaluated atazanavir alone, and the remaining 4 studies evaluated atazanavir alone and in combination with other agents. AI424021 and AI424039 evaluated only the atazanavir 400 mg QD regimen (not higher doses). In these two studies, linear regression analyses of QTc changes from baseline on Cavg (0-12 h) and Cmax of atazanavir, performed on the last day of administration of atazanavir alone, showed decreases in QTc changes from baseline for each additional 1000 ng/mL of Cavg (0-12h) and of Cmax. Study AI424040 was reviewed previously with results noted above.

PR results in studies AI424021 and AI424039 showed "mild concentration-dependent effects on the PR interval" with some development of first-degree AV block; the mean PR value was greatest around the time of maximum atazanavir plasma concentration. No 2nd or 3rd degree AV block was noted.

Out of 182 subjects given atazanavir alone in these 7 studies (From Table 3.2.2.1A, page 424), 39 were noted to have PR > 200 msec (indicating 1st degree AV block), the highest number occurring in study AI424040 (which used the 800 mg QD dosing); 2 subjects had > 60 msec change in QTc, and no subject developed QTc prolongation (defined as male >450 msec, female > 470 msec). When atazanavir was coadministered with ritonavir (study AI424056), 5 subjects developed change from baseline in QTc > 60 msec.

2. Protocol AI424-034:

Title: A Phase III Study Comparing the Antiviral Efficacy and Safety of BMS-232632 with Efavirenz; Each in Combination with Fixed Dose Zidovudine-Lamivudine (date: September 5, 2000)

Sites: Approx. 92 (multinational, including US)

Sample Size: 950 screened/enrolled to provide 800 randomized/750 evaluable patients.

Study Population: HIV-infected antiretroviral-naïve adults

Primary Objective: Compare antiviral activity of the two treatment arms at Week 48, defined as comparison of the proportion of subjects responding to treatment with HIV RNA levels < 400 c/mL for the BMS-232632/EFV placebo/ZCV-3TC arm vs the EFV/BMS-232632 placebo/ZDV-3TC arm

Study Summary: This is a double-blind, randomized, double-dummy, active-controlled, 2 arm study of BMS-232643 compared to EFV each in combination with ZCV-3TC over 48 weeks. According to the study design, eligible patients will be randomized (1:1) to triple therapy containing BMS-232632 400 mg QD/placebo EFV QD/ZCV-3TC 300 mg/150 mg BID or EFV 600 mg QD/BMS-232632 placebo QD/ZDV-3TC 300 mg/150 mg BID. Only one dose of BMS-232632 will be studied in this trial (section 5.5.2. contains prespecified language for dose reduction to 200 mg QD in the case of hyperbilirubinemia; the drug will be taken with a light meal or snack. Concomitant medications associated with CYP 3A4 metabolism regulation are contraindicated (per Appendix 6). The primary safety outcome measure will be number and severity of adverse events, serious adverse events (clinical or laboratory) and time to treatment discontinuation. The laboratory test section (5.9) and flow chart (1.1) do not include 12-lead EKG testing; however, in Amendment 2 (dated August 2, 2001) the sponsor notes, from study AI424-040, Three routine 12-lead EKGs for all subjects were added at the next study visit after approval of this protocol amendment. Timing of these EKGs were as follows: prior to medication, 2-3 hours post-dose, and 6-12 hours post-dose. EKGs were to be read centrally; PK sampling was also added for any subject requiring dose reduction. Withdrawal criteria was changed to include: QTc > 500 msec, heart rate < 50 bpm, pause > 3 seconds, third degree heart block or clinical symptoms potentially related to heart block.

3. Response to FDA Facsimile Dated January 29, 2002: PR and QT Interval Prolongation:

According to the sponsor:

- Atazanavir was tested for HERG activity using patch-clamp and was found to have modest activity at high doses. Several comparator HIV protease inhibitors had more significant HERG activity with the rank order of potency nelfinavir > saquinavir > lopinavir > ritonavir > indinavir ~ atazanavir.
- Metabolites: two pharmacologically inactive metabolites have been identified in human circulation, each of which constitute approximately 10% of plasma radioactivity.

- Atazanavir has been evaluated up to a dose of 800 mg QD, which produces exposures about 3-fold greater than that produced by a standard 400 mg dose. When atazanavir has been coadministered with low dose ritonavir, a CYP 3A4 inhibitor, the combination often increased the exposure of atazanavir 2-3 fold over a similar dose of atazanavir alone. An atazanavir/ritonavir 300 mg/100 mg QD regimen is currently being evaluated in a Phase III study (AI424045). Another study (AI424040) has used atazanavir at a dose of 800 mg QD.
- In study AI424040, 1/22 subjects on 800 mg QD was noted to have a borderline QTc (431-450 msec) ; in study AI424056, 2/21 subjects receiving atazanavir 300 mg/ritonavir 100 mg were noted to have at least one QTc between 431-450 msec. No subject in these studies developed a prolonged QTc (defined as > 450 msec for males, > 470 msec for females).
- When the QTc change from baseline was measured, 8/22 (36%) of those receiving atazanavir 800 mg QD in study AI424040 were noted to have at least one change in QTc value between 30-60 msec. In a group receiving 300 mg atazanavir/100 mg ritonavir daily for 10 days (study AI424056), 16/28 (57%) of subjects were noted to have at least one change in QTc value between 30-60 msec, and 5 subjects developed a change in QTc > 60 msec.
- The sponsor plans to perform a placebo-controlled study in healthy volunteers to assess cardiac risk potential, perhaps including an 800 mg dose of atazanavir, and anticipates available data post-registration.
- Also noted is a coefficient of variation of 40%, even in the presence of food (which increases exposure and lowers variability).
- In Attachment 1, page 22 (sponsor's conclusions), the sponsor notes that prolongation of the QTc interval (by Bazett and Fridericia) appear to be associated with the 800 mg QD dose of atazanavir.

ISSUES & COMMENTS:

1. **Question #1: Is there a significant risk for development of tdP with the two atazanavir dosing regimens (400 mg once daily, and atazanavir 300 mg / ritonavir 100 mg once daily)?**
 - a) **QTc prolongation:** Evidence for effects on QTc prolongation include: 1. Effects on APD in the rabbit Purkinje fiber study; and 2. QTc analyses. The sponsor notes "dose dependent and concentration dependent increase in the QTc interval", noting that QTc prolongation is seen with the 800 mg QD dose. It can be said that QTc prolongation would constitute a safety risk; obviously, this safety issue would need to be balanced against benefits in the HIV population.
 - b) **A remaining concern, therefore, is the characterization of safety risk.** If we believe that a risk is present at 800 mg QD, then there will also be a risk at 400 mg QD. If the event rate, based on 1,000 patients exposed, is zero, then the reviewer makes the assumption that the risk is less than 1%. However, the risk may change if the exposed patient population takes atazanavir under different conditions than the study population; hence, it is recommended that your Division explore and define the safety risk. Since we already know that there is a concentration-dependent increase in QT, this reviewer is concerned about conditions that will increase serum concentration (eg, food effects and concomitant medication). Since this drug is a 3A4 substrate, how will the ritonavir combination affect the QT interval? Will ketoconazole (a known 3A4 inhibitor) be excluded in this patient population?
 - c) **Suggestions about labeling:** If atazanavir were to be approved for the treatment of HIV, this Division will be glad to assist you with specific suggestions regarding cardiovascular labeling (for QT and PR intervals) after the data have been reviewed and risk-benefit considerations have been weighed. Your options for labeling include:
3. **PR interval prolongation:** The available data suggest that there is a dose-related PR interval prolongation. The mechanism (whether a direct effect on the AV node, or an indirect autonomic effect) is unclear. Preclinical data suggest an effect on calcium channels, which might be the mechanism for PR interval prolongation. It is unclear whether or not there are also vagal-mediated effects (ie, HR changes/other vagal effects). This reviewer might be concerned about higher grades of AV block, particularly in patients with underlying conduction system disease (who are unable to mount a junctional escape rhythm). This reviewer anticipates that such cases will be rare in the pivotal trials, given your current database; typically these patients are elderly or have underlying heart disease. However, myocarditis and cardiomyopathy (whether related to HIV or associated opportunistic infection) have been seen in this patient population; the effects of this drug on the conduction system in this particular group are unknown. Your Division (and the Sponsor) should still attempt

to understand the electrophysiologic effect of this drug on AV conduction and appropriate language should appear in labeling.

4. Recommendations (see below)

RECOMMENDATIONS:

- Your Division should evaluate this drug, with potentially important benefits in this patient population against safety risks; this reviewer would suggest a trial with morbid-mortal outcomes in order to facilitate this decision.
- Since there is a potential safety issue with atazanavir 800 mg QD dose (QTc prolongation), and this drug has the features of high variability coefficient, food effect and CYP 3A4 metabolism, this reviewer is concerned about conditions that might produce high serum concentrations of atazanavir, even with the proposed dosing regimen, and suggests interaction studies (for example, an atazanavir/ritonavir/food/ketoconazole study) that produce high serum concentrations with appropriately timed 12-lead EKGs. This reviewer agrees with the addition of EKG monitoring to ongoing clinical trials; in particular, EKGs should be timed with Cmax where possible.
- Attention should be paid toward effects on heart rate (as heart rate changes affect QT interval).
- Does this drug cause lowering of electrolytes (potassium, magnesium, calcium) which might in turn affect QTc?
- If atazanavir is under consideration as "second-line" therapy, you might consider a clinical trial in patients who have failed other protease-inhibitors.

Thank you. If you have any further questions or comments, please feel free to contact this Division.

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